RESEARCH ARTICLE

A Randomized Controlled Clinical Study of Sublingual, Vaginal, and Rectal Misoprostol for the Management of First Trimester Missed Abortions

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ABSTRACT

Objective: Miscarriage is one of the most frequent medical conditions that a woman will face during her life. The study's aim was to determine the efficacy and safety of sublingual, vaginal, and rectal misoprostol for ending pregnancy in women who had a missed first-trimester miscarriage. **Methods:** An open label, parallel group, randomized clinical trial was conducted in a university hospital between April 1, 2019,and September 30, 2021. All women who had a missed abortion in the first trimester were invited to participate in the study and were randomly assigned to one of three groups: one received rectal misoprostol in three 600 mg doses every four hours, while the other two received sublingual or vaginal misoprostol in the same dosing regimen. The primary outcome of the research was the rate of complete abortion within 7 days of beginning treatment. **Results:** The research included 210 women (70 in each arm). On day 7, the sublingual (72.4%) and vaginal misoprostol groups (75.3%) had a significantly greater percentage of successful complete abortion (p =.007) than the rectal misoprostol group (57.1%). Although there was no statistically significant difference between the sublingual and vaginal misoprostol groups at day 30, the sublingual and vaginal misoprostol groups had a higher percentage of complete abortion (92.5% -94.0%) than the rectal misoprostol group (75.7%). Sublingual misoprostol adverse effects were significantly more prevalent than vaginal and rectal misoprostol side effects. **Conclusion:** Sublingual and vaginal misoprostol are more effective than rectal misoprostol for completing missed abortions in the first trimester, and they require less time to induce and evacuate. When compared to vaginal and rectal misoprostol, sublingual misoprostol has more side effects, such as an unpleasant taste, gastrointestinal issues, and fever.

Key words: Sublingual, misoprostol, missed abortion, miscarriage.

INTRODUCTION

When a fetus stops growing or dies without displaying indications of miscarriage, such as blood or discomfort, it is called a missed miscarriage. When the baby stops growing but the sac remains intact, the body continues to produce hormones that make women feel pregnant, this is known as a missed miscarriage. (1)

Miscarriage rates among known pregnant women range from 10 to 20%, whereas rates among all fertilized zygotes range from 30 to 50%. (2). Women who have experienced a first-trimester miscarriage with ultrasound evidence can be treated expectantly, medically, or surgically (3).

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First trimester miscarriage has historically been treated with surgical uterus evacuation because to the danger of uterine infection and bleeding. Even if no therapy is provided, it is now known that the risk of infection or bleeding in spontaneous abortion is negligible (4). There are several medical treatment options accessible. The major pharmacological agent is misoprostol, which can be taken alone or with the anti-progestogen mifepristone. According to recent studies, misoprostol alone is as effective as a combination of mifepristone and misoprostol and is more cost-effective (5).

Rectal misoprostol has a three-fold higher systemic bioavailability than oral misoprostol, according to studies (6). Vaginal misoprostol pills have been linked to inconsistency in absorption (which can be addressed by dissolving the tablets in water), incomplete absorption (even several hours after delivery), and discomfort following vaginal administration (7). When a rapid start to clinical action is necessary, such as postpartum hemorrhage or cervical priming, sublingual misoprostol may be useful. Vaginal misoprostol, on the other hand, is useful for situations when clinical symptoms take longer to manifest, such as medical abortion. It has a high bioavailability and a sustained blood level. (8)

Because of its high absorption, recent studies show that the sublingual route of misoprostol administration is the most effective (9).Misoprostol taken sublingually is reported to attain the highest peak plasma concentration in the shortest amount of time (10).

The goal of this research was to evaluate the effectiveness and safety of misoprostol administered sublingually vs rectally for the completion of a missed first-trimesterabortion.

MATERIAL AND METHODS

Study Type, Setting, and Duration

We conducted an open label randomized controlled research on 210 pregnant women attending the outpatient clinic at Aswan University Hospital in Aswan, Egypt, from April 1, 2019, to September 30, 2021. After the institutional review board (Aswu/297/9/19) accepted the research protocol.

Study Participants

We offered each participant a thorough description of the study's purpose and methods. Before the trial began, eligible patients who were invited to participate in the study in case presented with first trimester missed abortiongave written informed consents.

Pregnant women with a gestation of <12 weeks and a missed abortion verified by ultrasound performed by two independent sonographers met the inclusion criteria. Women who were hemodynamically unstable, had a fever or suspected sepsis, severe anemia, or a history of bronchial asthma were excluded from the study, as were women who were receiving anticoagulation for any reason, women who had a known allergy to misoprostol, and women who had a history of failed medical or surgical pregnancy termination. All the women who were recruited had their medical histories taken (including their age, parity, and gestational age), as well as a general and obstetric checkup.After describing the nature of the study, including the potential adverse effects of misoprostol, informed consent was acquired for participation.

Randomization and Allocation

210 women who had missed an abortion in the first trimester were divided into three equal groups based on computer-generated random numbers. The allocation sequence was established by a separate individual. Each lady received an order, and the medication was sent with a code that corresponded to her envelope number. We randomly assigned women to receive misoprostol, either sublingually, vaginally, or rectally, in addition to their usual therapy.

Intervention

Women who met the criteria were randomly assigned to one of three groups: sublingual (group I), vaginal (group II), or rectal (group III) misoprostol. Each group received three doses of misoprostol 600 mg every four hours, given sublingually, rectally, or vaginally. Each misoprostol dosage consisted of three 200 mg pills (Misotac; Sigma Pharmaceuticals, Cairo, Egypt).

The initial dosage of misoprostol was given at the hospital shortly after the women were admitted to the trial, and they were kept under supervision for one hour in case of any side effects.

The ladies were instructed to record the precise time of each self-medication for the second and third dosages, which were given to them at home. A study kit containing two doses of misoprostol 600 mg each, four paracetamol 500 mg tablets as an analgesic or antipyretic if needed, two pairs of disposable gloves, and a pictorial blood loss assessment chart to quantify the amount of bleeding was given to each woman in addition to verbal instructions.

Patients were told to go to the emergency room if they had significant bleeding. A simple example is soaking two maxi

sanitary pads every hour for two hours in a row. Furthermore, if the products of conception were passed out, patients were told to skip the third dosage of misoprostol. Patients were given a specimen jar to collect the materials of conception if they passed out.

Follow up

On day 7, the initial follow-up appointments included hemoglobin testing and transvaginal ultrasound to evaluate endometrial thickness. The duration of bleeding, the timing of transit of products of conception, and the presence of adverse effects were also documented (fever, shivering, nausea, vomiting, diarrhea, unpleasant taste).

The distance between the echogenic interfaces of the endometrium and myometrium across the central longitudinal axis of the uterine body, at the junction of the upper one-third and lower two-thirds of the endometrial cavity, was used to determine endometrial thickness.

Patients who had a retained gestational sac were given a second round of misoprostol at the same dose as previously. Unless there was significant bleeding or indications of pelvic infection, no further action was taken.

On the 14th day after starting the first misoprostol dose, a second follow-up appointment was scheduled. This appointment included a bleeding assessment as well as a transvaginal ultrasound to determine whether any retained products of conception were present. Variable echogenic or heterogeneous material inside the endometrial cavity, an intrauterine mass, or thicker endometrium with vascularity by color flow Doppler are the ultrasonographic findings. Patients with a retained gestational sac after 14 days had surgical evacuation.

On day 30, the ultimate decision on partial abortion would be made. Up until day 30, if no emergency or voluntary evacuation was required, the result was classed as complete abortion. The necessity for surgical evacuation was defined as the need for surgery owing to technique failure (retained gestational sac on day 14 or endometrial thickness >15 mm on day 30) or heavy bleeding.

Study Outcomes

The major outcome measure was the rate of complete abortion within 7 days of starting therapy, which was defined as visual inspection of the products of conception being expelled and verified by ultrasonography as a clean, thin endometrium on day 7. The rate of complete abortion at 14 and 30 days; the mean time between the initial misoprostol dose and complete abortion (induction–expulsion interval); the rate of treatment failure; the need for analgesia; the need for surgical evacuation in cases of incomplete abortion; the bleeding pattern after misoprostol intake; and the occurrence of side effects were all secondary outcomes.

Sample size

The sample size was calculated using data from one trial (10), which found a 72 percent probability of complete abortions 24 hours after vaginal misoprostol treatment. The overall sample size was determined to be at least 210 individuals (70 in each research arm) with 85 percent power to detect a 20% difference between groups (odds ratio 4.6) assuming a 10% rate of loss to follow-up using a two-sided v2 test with a significance threshold of 0.05. (Epi Info; Atlanta, GA: Centers for Disease Control and Prevention)

Statistical Analysis

The Statistical Package for Social Sciences ((SPSS, Chicago, IL, USA).) version 16 was used to enter data and perform statistical analysis. Numbers and percentages were used to describe qualitative data. The Chi-square test and the Monte Carlo test were employed to compare groups, when needed. Quantitative data were expressed as means (SD) or medians, depending on the situation. The Kolmogorov-Smirnov test was used to determine their normalcy. A one-way ANOVA test with LSD post-hoc multiple comparisons was performed for comparison between groups in the normally distributed variables, if applicable. The Mann Whitney test and the Kruskal-Wallis test were employed to compare groups in non-normally distributed data, where applicable. We estimated odds ratios and their 95% confidence intervals. The statistical significance of "p-value 0.05" was established.

RESULTS

210 women agreed to participate out of 230 eligible women who attended at our institution with a missed first trimester abortion. Eleven women were unable to participate due to ineligibility, while nine others withdrew. The remaining 210 women were randomly assigned to one of three research groups. Misoprostol was given sublingually (group I), vaginally (group II), or rectal (group III) to consenting women at random. (See Figure 1 for a flowchart of the research)

There were no significant differences in age, weight, height, BMI, parity, gestational age, first hemoglobin, or temperature between the two groups. (Table 1)

By day 7, successful complete abortion was significantly more

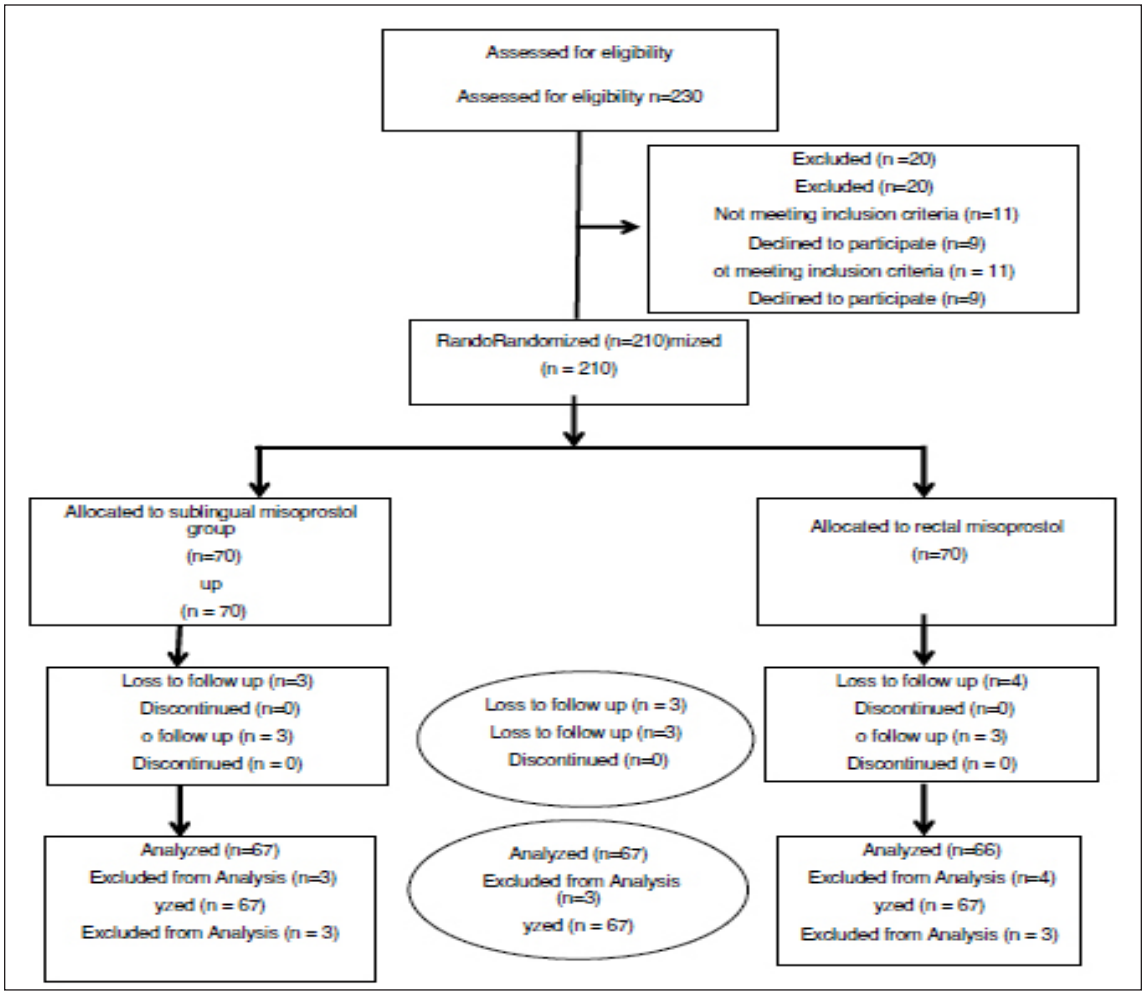

Figure 1: Consort flowchart showing enrollment of participants

Table 1: Baseline Characteristics of Pregnant Women in the Study Groups

Parameters	Group I (n = 70)	Group II (n = 70)	Group III (n = 70)	Significance
Age (year)	29.5 ± 2.42	29.6 ± 2.68	29.83 ± 2.85	0.854
Weight (kg)	69.25 ± 7.76	69.43 ± 7.18	69.4±7.77	0.994
Height (cm)	162.45 ± 4.19	163.58 ± 4.38	163.52 ± 4.6	0.436
BMI	26.1± 2.55	25.46 ± 2.74	25.94 ± 2.71	0.888
Parity (median) (Minimum – maximum)	3 (0 – 4)	2 (0 – 5)	3 (0 – 5)	0.866
Gestational age (weeks)	9.4 ± 1.45	9.55 ± 1.34	9.5 ± 1.22	0.878
Initial Hemoglobin	10.97 ±0.624	10.98 ± 0.623	10.83 ± 0.622	0.905
Primigravida	31	30	29	0.965
Multiparous	39	40	41	0.965

BMI (body mass index), CS (Cesarean Section), CPD (cephalopelvic disproportion)
Variables are presented as mean and standard deviation, median (minimum – maximum) and number (percentage)

frequent among the sublingual misoprostol group (72.4%) and vaginal misoprostol(75.3) than among the rectal misoprostol group (57.1%) (p = .006); the success rate increased with increasing duration of follow-up (days 14 and 30).

By day 30, the rate of complete abortion was higher among the sublingual (92.5%) and vaginal misoprostol group (94%) than among the rectal misoprostol group (75.7%); however, the difference was not statistically significant (p ¼ .164) (Table 2).

The mean length of the induction–expulsion interval in the sublingual and vaginal misoprostol group was significantly shorter than in the vaginal misoprostol group (18.3 ± 3.1vs 19.4 ± 4.2, vs26.4 ± 4.2 respectively).

Duration of bleeding following treatment in the sublingual misoprostol group was not significantly different from the vaginal or rectal misoprostol group (p= 0.731)

The number of women with a retained gestational sac or retained products of conception needing surgical evacuation did not differ significantly across the three groups (p 0.01). Furthermore, there was no significant difference in the medical treatment failure rate between the sublingual and vaginal groups (7.4% vs 5.9%; p =0.861). (Table 2).

Table 2: Primary and Secondary Outcome Variables in the Three Groups

Blood loss	Group I Sublingual miso	Group II Vaginal miso	Group III rectal	Significance
Complete abortion by day 7	50/69 (72.4)	51/69 (75.3)	40/70 (57.1)	0.007* 0.861 / 0.01*/ 0.01*
Complete abortion by day 7	60/68 (88.2)	60/67 (89.5)	47/67 (70.1)	0.0001* 0.926 / 0.001*/ 0.001*
Complete abortion by day 30	62/67 (92.5)	63/67 (94.0)	50/66 (75.7)	0.01* 0.12/0.001*/ 0.001*
Induction–expulsion interval, h	18.3 ±3.1	19.4 ± 4.2	26.4 ± 4.2	0.001* 0.726 / 0.001*/ 0.001*
Duration of bleeding, days	14.6 ± 2.5	15.2 ±2.9	17.2 ± 2.9	0.731
Failure rate of medical Treatment	5/67 (7.4)	4/67 (5.9)	16/66 (24.2)	0.001* 0.861 /0.001*/ 0.001*
Hemoglobin level at day 7, g L)	10.17 ± 0.513	10.18 ± 0.521	9.93 ± 0.722	0.866

* Statistically Significant Difference (Group I Versus GroupII / GroupI Versus Group III / Group II Versus Group III)
# Variables are presented as mean and standard deviation, and number (percentage).

The reduction in hemoglobin level following treatment in the sublingual misoprostol group was not significantly different from the vaginal or rectal misoprostol group (p= 0.866). In addition, there was no significant difference in the requirement for analgesia across the research groups. Finally, when comparing the sublingual misoprostol group to the vaginal and rectal misoprostol groups, adverse effects were considerably more common in the sublingual misoprostol group. (See Table 3)

Table 3: Adjuvant Interventions and Side Effect Measurements

Variables	Group I Sublingual miso	Group II Vaginal miso	Group III rectal	Significance
Need of anesthesia	17(13.4)	8(11.9)	8(12.1)	0.001* 0.001*/ 0.001*/ 0.814
Shivering	--	--	--	----
pain	11(50)	5 (12.5)	4 (7.5)	0.0001* 0.0001*/ 0.0001*/ 0.214

Unpleasant taste	12(20)	2	1	0.0001* 0.0001*/ 0.0001*/ 0.672
Fever (%)	8(6.6)	1(6.6)	1(6.6)	0.0001* 0.0001*/ 0.0001*/ 0.214
Nausea (%)	14 (4.4)	4(6.6)	3(6.6)	0.001* 0.001*/ 0.001*/ 0.321
Vomiting (%)	7(2.2)	1(2.2)	2 (4.4)	0.001* 0.001*/ 0.0001*/ 0.214
Diarrhea (%)	3(2.2)	1(2.2)	1(6.6)	0.620

*Statistically Significant Difference (Group I Versus GroupII / GroupI Versus GroupIII / GroupII Versus GroupIII)
Variables are presented as mean and standard deviation and number (percentage)

DISCUSSION

Sublingual misoprostol (600 mg every 4 hours in three doses) was found to be more effective than rectal misoprostol (600 mg every 4 hours in three doses) and comparable to vaginal misoprostol (600 mg every 4 hours in three doses) for completing first trimester missed abortion within 7 days after administration; however, it was associated with more side effects and the need for a second procedure. Medical therapy for missed abortions has been found to reduce the need for surgical evacuation, is less costly, and is associated with high patient satisfaction. (9)

The purpose of this study is to evaluate the safety and effectiveness of sublingual misoprostol vs vaginal and rectal misoprostol in the medical treatment of missed abortions in the first trimester. Sublingual and vaginal misoprostol is thought to be more successful than rectal misoprostol, requiring fewer doses for conceptus ejection, but misoprostol sublingual show certain adverse effects.

Several studies have looked at the optimal first-trimester abortion medical care regimen, including dose (single or repeated), method, and timing of follow-up. Slower absorption, lower peak plasma levels, more drug exposure and impact on the cervix, and a reduced risk of gastrointestinal adverse effects have all been linked to vaginal misoprostol delivery (11,12).

Our results agree with those of Tanha et al. (13), who found that sublingual misoprostol 400 lg every 6 h was significantly more effective than the same dosage of vaginal misoprostol (84.5% vs 46.4%; RR 0.54; 95% CI 0.442, 0.681).

Shah et al. discovered that the mean times to expulsion were similar in both groups (13.07 6.95 h for sublingual versus 13.29 5.63 h for vaginal) (14), while Tanha et al. discovered that the mean time to expulsion in the sublingual group was shorter (9.68 h, SD = 5.51, 95 percent CI = 8.61–10.57) than in the vaginal group (16.64 h, SD = 14.01, 95 percent CI The discrepancy between the previous two trials and this research in terms of fast vaginal effect is due to the fact that the previous two studies utilized greater dosages of misoprostol than the current study.

Sharma et al. (15) reported an overall success rate of 86 percent with sublingual misoprostol 600 mg every 3 hours. Ng et al. (16) reported a 92 percent overall success rate with vaginal misoprostol 800lg every 8 h in three doses using an endometrial thickness of 15 mm; however, their study included women with incomplete abortion, which may explain the high success rate. The definition of success is a topic of contention in several published studies of medical treatment of early abortion. Some studies utilized a transvaginal ultrasonography-measured endometrial thickness of 15 mm as a success cutoff (17).

All the participants in our research had vaginal bleeding after misoprostol was inserted. Patients self-reported the number of pads used, the degree of soaking, and the quantity and size of daily blood clots in the PBLAC. This allowed us to identify the timing of passage of the productof pregnancy, which generally corresponded to the peak blood loss, as well as the length of bleeding. The sublingual misoprostol group had somewhat shorter bleeding times than the vaginal and rectal misoprostol groups, although the difference was not statistically significant (p=0.731).

Pain, shivering, nausea, vomiting, diarrhea, and an unpleasant taste were more prevalent in the sublingual misoprostol group than in the vaginal misoprostol group in the current research. The increased absorption of sublingual misoprostol might explain this.

One study(18) also found that 63.9 percent of the sublingual misoprostol group had an unpleasant taste, compared to 37.5 percent of the vaginal misoprostol group (p14.02). Other adverse effects, including as shivering, low-grade fever,

nausea, and diarrhea, were more common in patients taking sublingual misoprostol in our research; nevertheless, most patients regarded the side effects acceptable and transitory, and they gradually faded after the first day of therapy.

Our study's primary advantages are that it was randomized and that it used a large sample size to assess the efficacy of misoprostol. However, it does have certain restrictions. To begin, all patients self-reported that they took their misoprostol as prescribed. However, we can't rule out the likelihood of inaccurate self-reporting, which might be the study's worst flaw. Furthermore, we were unable to measure patient satisfaction since participants were not blinded to the delivery route, and treatment result may influence choice and pleasure with that route.

CONCLUSION

Sublingual and vaginal misoprostol are more effective than rectal misoprostol for completing missed abortions in the first trimester, and they require less time to induce and evacuate. When compared to vaginal and rectal misoprostol, sublingual misoprostol has more side effects, such as an unpleasant taste, gastrointestinal issues, and fever.

ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (Aswu/297/7/19).

The study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHORS CONTRIBUTION

NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation. HF: manuscript preparation.

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